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10/519,647	01/10/2006	Robert F. Kelley	P1966R1	7400

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,647	KELLEY ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-14,16-28 and 30-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-14,16-28 and 30-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 07 July 2009 has been entered in full. Claims 1, 2, 8-10, 14, 16, 17, 21-23, 26, 28, 31, and 33 amended. Claims 3, 6, 15, 29, and 34-38 are cancelled.

Claims 1, 2, 4, 5, 7-14, 16-28, 30-33 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejections of claims 1, 2, 4, 5, and 7-33 under 35 U.S.C. § 112, second paragraph as set forth at pages 2-3 of the previous Office Action (07 January 2009) are *withdrawn* in view of the amended and cancelled claims (07 July 2009).

2. The provisional rejection of claims 1, 2, 4, 5, and 7-33 under 35 U.S.C. § 101 as claiming the same invention as that of claims 1, 2, 5, 6, and 7-33 of copending Application No. 11/541,821 as set forth at pages 3-4 of the previous Office Action (07 January 2009) is *withdrawn* in view of the restriction election in the '821 application. The elected claims are directed to a method of using the Apo-2 ligand variant polypeptide.

3. The rejections of claim 29 under nonstatutory obviousness-type double patenting, 35 U.S.C. § 112, first paragraph (written description and scope of enablement), and 35 U.S.C. § 102(b) as set forth at pages 4-19 of the previous Office Action (07 January 2009) are *withdrawn* in view of the cancelled claim (07 July 2009).

4. The rejection of claim 15 under 35 U.S.C. § 112, first paragraph (scope of enablement) as set forth at pages 10-18 of the previous Office Action (07 January 2009) is *withdrawn* in view of the cancelled claim (07 July 2009).

Double Patenting

Nonstatutory obviousness-type double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 23-25, and 31-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-10, 12-13, 19-22, 24-39, 42-48, 58-67, and 81-82 of copending Application No. 11/541,828. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. The basis for this provisional rejection is set forth at pages 4-5 of the previous Office Action of 07 January 2009.

6. Claims 1, 23-28, 30-33 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 68-70 and 82 of copending Application No. 12/283,351. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) in Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C. It is noted that claims 1, 7-10, 12-22, 24-29, 42-48, 58-67 and 81 of the '351 application were included in the rejection of the previous Office Action of 07 January 2009. However, Applicant has since cancelled those claims in the '351 application.

At the bottom of page 7 of the Response filed 07 July 2009, Applicant acknowledges the provisional rejection and requests the rejection be held in abeyance until such time as a notice of allowance is issued for the subject claims.

The rejections are maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit terminal disclaimers at Applicant's earliest convenience.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 9, 22-28, 30-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 1, 9, and 22-33 at pages 6-10 of the previous Office Action of 07 January 2009.

Claim 1 is directed to an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more of the following amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1): S96C; S101C; S111C; R170C; K179C, wherein said variant binds DR4 receptor or DR5 receptor. Claim 9 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) selected from the group consisting of: Y189A:R191K:Q193K, Y189A:R191K:Q193K: H264R, Y189Q:R191K:Q193R: H264R:I266L:D267Q, Y189A:R191K:Q193K: H264D: I266L:D267Q: D269E, and Y189A:R191K:Q193R:H264S:I266L:D269E. Claim 22 recites an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) and has a set of amino acid substitutions at the residue position(s) of the Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO: 1) selected from the group consisting of:Y189Q:R191K:Q193R; H264R; I266L;

D267Q ; Y189Q:R191K:Q193R; and Y189Q:R191K:Q193R:I266L. Claim 28 recites a host cell comprising a vector.

At page 8 of the Response, Applicant argues that the disclosure provides numerous working examples of Apo-2 ligand variant polypeptides along with comprehensive description of the native human Apo-2 ligand polypeptide and how such polypeptides may be mutated and tested for biological properties and activities. Applicant asserts that the experimental data provided in the disclosure clearly demonstrates Applicant was in possession of the claimed embodiments.

Applicant's arguments (07 July 2009) have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the phrase "an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) **and** has one or more of the following amino acid substitutions" (recited in claims 1, 9, 22; emphasis added by Examiner) has been interpreted by the Examiner as reading upon Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 264, 266, 267, and 269. The specification of the instant application teaches that Apo-2 ligand variant polypeptides with specific amino acid substitutions are generated and the apoptotic activity of the native and pegylated variants is measured (pages 65-67, Example 8; page 69, Example 11; Figure 9). The specification discloses that PEG-R170C-Apo2L and PEG-K179C-Apo2L variants are cleared more slowly in the mouse than Apo2L.0 (page 69, Example 12). The claims of the instant application do not require that the Apo-2 ligand variant polypeptides possess any

particular conserved structure. Thus, the claims are drawn to a genus of polypeptides and nucleic acids encoding such. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. However, in this case, the specification fails to disclose and there is no art-recognized correlation between the structure of the genus of polypeptides (and claimed nucleic acids) and their function of binding to DR4 receptor, binding to DR5 receptor, or inducing apoptosis in a mammalian cell. The specification does not teach which amino acids can vary from SEQ ID NO: 1 and still result in a protein that retains activity. Therefore, the description of a few Apo-2 ligand variant polypeptides with specific amino acid substitutions and nucleic acids encoding such is not adequate written description of an entire genus of functionally equivalent polypeptides and nucleic acids.

Regarding Applicant's argument that specification provides a comprehensive description of the native human Apo-2 ligand polypeptide and how such polypeptides may be mutated and tested for biological properties and activities, the broad brush discussion of making and screening for Apo-2 ligand polypeptide variants does not constitute a disclosure of a representative number of members. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants. It is also noted that Applicant has not provided the Examiner with any specific evidence or disclosure from the specification to support Applicant's argument.

8. Claims 1-2, 4-5, 7-14, 16-28, 30-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated Apo-2 ligand variant polypeptide comprising one or more amino acid substitutions in the native Apo-2 ligand polypeptide amino acid sequence of SEQ ID NO: 1, wherein said one or more amino acid substitutions is selected from the group consisting of S96C, S101C, S111C, R170C, K179C, and H264C (and a nucleic acid molecule encoding such) *does not reasonably provide enablement for* an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) and has one or more amino acid substitutions. The specification is not enabling for Apo-2 ligand variant polypeptides that comprises one or more amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, and 269 of the native Apo-2 ligand sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 1, 2, 4, 5, and 7-33 at pages 10-18 of the previous Office Action (07 January 2009).

Applicant's arguments (07 July 2009), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 8 of the Response, Applicant asserts that the claims have been amended, without prejudice or acquiescence in an effort to advance the prosecution of the application. Applicant indicates that the claims are enabled across the full scope of the claimed subject matter.

Applicant's argument has been fully considered but is not found to be persuasive. Applicant's arguments and claim amendments have not addressed the issues that were discussed at part (i) of the enablement rejection in the previous Office Action. Specifically, the

specification of the instant application teaches that Apo-2 ligand variant polypeptides with specific amino acid substitutions are generated and the apoptotic activity of the native and pegylated variants is measured (pages 65-67, Example 8; page 69, Example 11; Figure 9). The specification also discloses that PEG-R170C-Apo2L and PEG-K179C-Apo2L variants are cleared more slowly in the mouse than Apo2L.0 (page 69, Example 12). Example 13 of the specification discloses that PEG-R170C-Apo2L.0 and PEG-K179C-Apo2L.0 caused a greater reduction in human COLO205 tumor volume than the same dose of Apo2L in a mouse xenograft model (bottom of page 69 through page 70). However, the specification does not teach that Apo-2 ligand variant polypeptides with amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, 269 of the native Apo-2 sequence of SEQ ID NO: 1 have any function. Additionally, the phrase "an isolated Apo-2 ligand variant polypeptide comprising an amino acid sequence which differs from the native sequence Apo-2 ligand polypeptide sequence of Figure 1 (SEQ ID NO:1) **and** has one or more of the following amino acid substitutions" (recited in claims 1, 9, 22; emphasis added by Examiner) has been interpreted by the Examiner as reading upon Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 199, 201, 264, 266, 267, and 269. The specification does not teach any variant, fragment, or derivative of the Apo-2 ligand polypeptide other than the full-length amino acid sequences of SEQ ID NO: 1 with one or more amino acid substitutions selected from the group consisting of S96C, S101C, S111C, R170C, K179C, and H264C. The specification also does not teach any methods or working examples to demonstrate the functional characteristics of all the Apo-2 ligand polypeptide variants, fragments, and derivatives recited in

the claims. Undue experimentation would be required by the skilled artisan to determine such.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at

Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

The assumption that Apo-2 ligand variant polypeptides with amino acid substitutions at positions 189, 191, 193, 199, 201, 266, 267, 269 of the native Apo-2 sequence of SEQ ID NO: 1 bind DR4 receptor or DR5 receptor or that Apo-2 ligand variant polypeptides of SEQ ID NO: 1 with any number of deletions, substitutions, or additions *in conjunction with* one or more specific amino acid substitutions at positions 96, 101, 111, 170, 179, 189, 191, 193, 199, 201, 264, 266, 267, and 269 have a biological activity cannot be accepted in the absence of supporting evidence because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Wuyts et al. (J Immunol 163: 6155-6163, 1999) establish that NH_2-and COOH- terminal truncations of granulocyte chemotactic protein-2 (GCP-2) have enhanced neutrophil chemotactic potency as compared to wild-type GCP-2 (abstract; pg 6157-6158). Sher et al. (J Biol Chem 274(49):35016-35022, 1999) disclose that keratinocyte growth factor (FGF-7) acts predominantly on cells of epithelial origin and regulates processes in embryonal and adult development, including cell growth, differentiation, cell migration, and repair of epithelial tissues (pg 35016, ¶ 1). Sher et al. demonstrate that point mutations in a loop of FGF-7 do not alter receptor binding affinity, but cause reduced mitogenic potency and reduced ability to induce receptor-mediated phosphorylation events (pg 35020-35021). Additionally, a SCF mutant called $Steel^{17H}$ (Sl^{17H}) induces melanocyte defects and sterility in males. The Sl^{17H} allele contains a mutation that results in the substitution of 36 amino acids in the SCF cytoplasmic

domain with 28 novel amino acids (Kapur et al., Blood 94(6): 1915-1925, 1999). Kapur et al. teach that compound heterozygous Sl/Sl^{17H} mice manifest several hematopoietic abnormalities in vivo, such as red blood cell deficiency, bone marrow hyperplasia, and defective thymopoiesis (pg 1917-1918; Figures 2-3). In vitro, both the soluble and membrane-associated Sl^{17H} isoforms exhibit reduced cell surface expression on stromal cells and diminished biological activity as compared to wild soluble and membrane-associated forms (abstract, pg 1919-1921; Figures 6-7). Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Finally, Hymowitz et al. teach that the Apo-2 ligand structure represents the first example of metal binding-mediated trimerization of a cytokine, wherein alanine or serine substitutions of Cys230 or removal of the bound zinc metal indicate the zinc binding site is essential for full bioactivity (Biochemistry 39:633-640, 2000; page 635, column 2, 3rd full paragraph; page 637, column 1, last paragraph). Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, the specification fails to teach the skilled artisan how to make and use biologically active Apo-2 ligand variant polypeptides without resorting to undue experimentation to determine what the specific biological activities of the variants are.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention;

the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function; and the breadth of the claims which fail to recite any structural and/or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 2, 4-5, 8, 10, 12-13, 16, 17, 19-20, 26-28, 30, 31, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Hymowitz et al. (Biochemistry 39: 633-640, 2000). The basis for this rejection is set forth at page 19 of the previous Office Action (07 January 2009).

Applicant's arguments (07 July 2009), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 9 of the Response, Applicant contends that Hymowitz et al. do not teach or even mention the Apo-2 ligand variants provided for by the present application, not does Hymowitz et al. disclose that such variants can retain desired biological properties, such as receptor binding or apoptotic activity.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, Hymowitz et al. teach Apo-2 ligand variant polypeptides comprising amino acid

substitutions at positions 201, 264, or 269 in the native Apo-2 ligand polypeptide amino acid sequence of SEQ ID NO: 1 (and nucleic acid molecules encoding such) (page 637, Table 1; page 634, column 1). Hymowitz et al. teach mutants K201A, R191A, Q193A, H264A, D267A, and D269A, which are recited by claims 2, 10 and 17 of the instant application (see page 637, Table1 of Hymowitz et al.). Hymowitz et al. teach that the mutants are constructed by oligonucleotide-directed mutagenesis of a plasmid and that *E. coli* strain 294 is transformed with the mutated plasmids (page 634, column 1, first full paragraph). Hymowitz et al. disclose that the mutants are expressed and purified (page 634, column 1, first full paragraph). The bioactivity of the Apo-2 ligand mutants is determined by measuring the cell viability of SK-MES-1 human lung carcinoma cells in the presence of the mutants (page 634, column 2, 2nd full paragraph; Table 1, page 637). The K201A, R191A, Q193A, H264A, D267A, and D269A mutations only resulted in a 3.1-fold or less reduction in apoptosis as compared to wild-type Apo-2 ligand and the mutated proteins still bound DR4 and DR5 (see Table 1).

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
26 October 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647